II. NON-TECHNICAL ABSTRACT:

There are 15,000 new cases of primary brain tumor with 11,000 deaths annually in the United States, and brain tumors are the second leading cause of cancer death in children and young adults. Even with aggressive surgical and radiation therapies many patients with brain tumors have survival times of only 9 to 10 months. Hence, the prognosis for this disease is bleak and compels investigation of new therapeutic avenues.

Direct introduction of therapeutic genes into tumor cells may provide an effective treatment of brain tumors. One strategy is to confer drug sensitivity to tumor cells by inserting a recombinant gene into them. This gene is from the common Herpes virus and it codes for the enzyme thymidine kinase (HSV-tk) enzyme. Thymidine kinase converts the anti-viral drug ganciclovir into a form that is toxic to rapidly dividing cells such as tumor cells. Non-dividing are not harmed. This approach is especially suitable for the treatment of brain tumors since the normal brain tissue is made up largely of non-dividing cells. Several techniques have been used to introduce therapeutic genes to tumors. Of these, virus-mediated transfer is currently the most efficient method and the most efficient virus is the genetically engineered adenovirus. We have demonstrated using two animal models that adenovirus-mediated transfer of the HSV-tk gene and ganciclovir treatment resulted in ablation of the tumors and significant increases in life spans.

This phase I study is designed to study the safety and efficacy of gene therapy for patients with brain tumors. Patients with malignant brain tumors refractory to all potentially curative therapy will be treated with intra-tumor injections of replication-defective adenovirus vector delivering the Herpes Simplex Virus thymidine kinase gene. Initial tests will use a low dose of virus. Ganciclovir will then be administered intravenously at 10 mg/kg/day for 14 days. Only one course of therapy will be administered. Each patient will be carefully monitored for one month for adverse effects. Five patients will be tested with this low dose before another group of patients are treated with a higher dose and monitored closely for 1 month. This will be repeated until the target dose is reached or significant toxicity is detected. Effectiveness will be monitored by MRI and/or CT scans and by comparing survival times to the historical survival times for patients with recurrent brain tumors. The primary objective of this initial study is to determine whether the treatment is associated with significant toxicity.